Ethylene Glycol Monohexyl Ether

(CAS# 112-25-4)

(Synonyms: EGHE: ethylene glycol mono hexyl ether; ethylene glycol monohexyl ether; glycol monohexyl ether; Hexylcellosolve; Hexyl Cellosolve ®; n-Hexyl Cellosolve®; 2-hexyloxyethanol; 2-(hexyloxy)ethanol; ethanol, 2-(hexyloxy)-; n-hexylglykol; 3-oxa-1-nonanol: EGHE)

Ethylene glycol monohexyl ether (EGHE) 8-hour REL

Reference Exposure Level	**32 µg/m^3**
Critical effects	Decreased body weight
Hazard Index target	Systemic – decr maternal weight gain

1 Physical and Chemical Properties

Physical form	water-white liquid
Molecular Formula	$C_8H_{18}O_2$
Structural Formula	$HOCH_2\ CH_2OCH_2CH_2\ CH_2CH_2\ CH_2CH_3$
Molecular weight	146.23 g/mol
Density	0.89 g/cm^3
Boiling point	208ºC
Melting point	-45.1 ºC
Vapor pressure	0.05 mm Hg @ 25ºC
Flash point	90.56ºC
Log? P_{OW}	1.97
Solubility	slightly soluble in water; very soluble in alcohol and ether
Conversion Factor	1 mg/L= 168 ppm; 1 ppm = 5.98 mg/m^3

2 Production, Use, and Exposure

Ethylene glycol monohexyl ether (EGHE) is manufactured by reaction of ethylene oxide with 1-hexanol. The estimated manufacturing volume of EGHE in the United States according to the 2002 US EPA TSCA Inventory Update Report was 454 – 4,540 metric tons and the European production volumes (production, not capacity) in 2003 was <1000 metric tons (UNEP 2003). EGHE is sold by the Dow Chemical Company under the name Hexyl Cellosolve™ solvent (Dow 2007).

Uses for EGHE include: high boiling solvent (e.g., for surface coatings and cleaning solutions); coalescing agent in latex paints and cleaners; and chemical intermediate for hexyloxyethyl

phosphate and neopentanoate (UNEP 2003). EGHE is also used in specialty printing inks (Dow 2007).

Human exposure to EGHE occurs primarily via inhalation and dermal contact. Although most uses of EGHE are industrial and workplace, some consumer exposure may occur through the use of these chemicals in consumer products. Zhu et al. (2001) detected emissions of EGHE in three out of seven samples of consumer cleaning products. Consumer exposure to EGHE may also occur through the use of latex-based coatings (Dow, 2007). Exposures also occur during multiple uses of EGHE as solvents and coalescing aids in surface coatings, printing inks, adhesives and cleaners. Workplace exposure to EGHE in manufacturing operations may occur during maintenance, sampling, testing, or other procedures (Dow, 2007).

Consumer and general population exposure to environmental concentrations of EGHE may also occur. However, since EGHE does not persist in the environment, environmental concentrations are expected to be very low to negligible, except possibly near industrial operations using products containing EGHE (UNEP 2003). Environmental releases to the atmosphere and water do occur during manufacture, from process vents and aqueous streams, but aqueous waste streams are subject to in-plant biodegradative wastewater treatment. Environmental releases are expected to occur to a much greater extent during use of these chemicals as solvents and coalescing aids in coatings and printing ink formulations and in cleaners and adhesives. These emissions are primarily to the atmosphere through evaporation, and to a lesser extent to water. Although EGHE may be used as an industrial intermediate that is converted to other chemicals, all are solvents with wide, dispersive uses (UNEP 2003).

3 Pharmacokinetics and Metabolism

EGHE is a member of the monoetheylene glyol ether category. EGPE, EGBE, and EGHE are substrates for alcohol dehydrogenase isozyme ADH-3 in rat liver, which catalyzes the conversion of their terminal alcohols to aldehydes (which are transient metabolites) (Aasmoe et al., 1998). Further, rapid conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers and their acetates and the predominant metabolites responsible for the toxicities of the mono-substituted glycol ethers. At equivalent concentrations, metabolism of EGPE is less rapid than EGBE and more rapid than EGHE (UNEP 2003).

The respective Vmax (3.04, 5.78 and 1.66 nmol NADH/min/mg protein) and Km (0.23, 0.27 and 0.15 mM) values for EGPE, EGBE and EGHE varied as follows: EGBE > EGPE > EGHE. These data suggest that at equivalent concentrations metabolism of EGPE is less rapid than EGBE and more rapid than EGHE. The Km and Vmax for metabolism of EGHE by alcohol dehydrogenase are higher than values for EGPE and EGBE, suggesting that elimination of EGHE is somewhat slower than that of EGPE and EGBE (UNEP 2003).

Sulfate and glucuronide conjugation of the parent glycol ethers may occur, and glycine (rodents) and glutamine (humans) conjugates of the alkoxyacetic acid metabolites may also be produced, and their formation contributes to detoxification (UNEP 2003).

4 Acute Toxicity

4.1 Human Toxicity

Reports of acute, high-level human exposures are limited to extremely large ingestions, which caused CNS depression, renal injury, hyperventilation, hemolysis, and metabolic acidosis. The onset of symptoms may be delayed for up to 18 hours (HSDB, 2008). EGHE is severely injurious to the eye and can produce serious skin irritation if exposed to occluded skin or for prolonged periods of contact (Boatman and Knaak, 2001). Brief skin contact with EGHE may cause severe skin burns with symptoms including: pain, severe local redness, and tissue damage (Dow 2007). Prolonged skin contact may result in absorption of harmful amounts (Dow, 2007). EGHE is classified as corrosive to the skin according to the U.S. Department of Transportation (DOT) guidelines.

4.2 Animal Toxicity

Table 4.2.1. Acute toxicity of EGHE in rats or rabbits by inhalation, oral, and dermal routes

Inhalation (rats)	Oral (rats)	Dermal	Intravenous
LC_{50} 739 ppm	LD_{50} 1.48 g/kg-bw	LD_{50} (mg/kg-bw) 721 (rabbits) 790 (rats)	LD_{50} (mg/kg-bw) 53.6 (male rats) 70.0 (female rats 40.0 (male rabbits) 30.3 (female rabbits))

(Ballantyne et al., 2003, Smyth et al., 1954)

Dermal. EGHE was tested in rabbits after dermal administration. Signs of toxicity included salivation, sluggishness, unsteady gait, skin irritation and ulceration, and comatose appearance. EGHE caused slight to moderate, but reversible irritation to the skin. EGBEA appears to be less irritating to skin and EGHE more irritating to the skin than EGPE or EGBE (UNEP 2003). The dermal LD_{50} for rats was reported as 0.89 ml/kg-bw (790 mg/kg-bw) by Smyth et al. (1954) and 0.81 mL/kg and 0.93 mL/kg for male and female rabbits, respectively, according to Ballantyne and Meyers (1987). The onset of signs occurred approximately twenty to thirty minutes after application. A clear dose-response relationship for skin irritation was observed at concentrations of 44 mg/kg/day and higher (222 or 444 mg/kgb-w/day over an 11-day application period (Union Carbide 1989 as cited in Boatman and Knack 2001).

EGHE was studied in male and female New Zealand White rabbits by occluded epicutaneous dosing for nine days (Ballantyne et al., 2003). The epicutaneous doses were 0, 44, 222, and 444 mg/kg-d for 6 hours per day. Signs of local irritation, erythema, and edema, as well as exfoliation were observed. Dose-dependent decreases in body weight were also noted for the middle and high dose. The majority of EGHE-dosed animals had acanthosis, hyperkeratosis, and dermatitis, which was ulcerative at the middle and high doses (Ballantyne et al., 2003).

Oral. Single-dose oral LD_{50} values in rats for EGHE have been reported as 1.48 g/kg-bw by Smyth et al (1954), and 1.67 mL/kg (1490 mg/kg-bw) for male rats and 0.83 ml/kg-bw (740 mg/kg-bw) for females by Ballantyne and Myers et al. (1987). Clinical signs of toxicity in rats administered EGHE

by the oral route included sluggishness, unsteady gait, and prostrated appearance (UNEP 2003). Mucosal irritation occurred at 890 mg/kg-bw (Ballantyne and Myers et al., 1987).

Inhalation. In several studies, no signs of toxicity and no lethality were observed after inhalation exposure to saturated vapor at room temperature for 6 or 8 hours in male and female rats (Smyth et al., 1954; Ballantyne and Myers 1987).

4.3 Repeated Exposure Toxicity

Male and female F344 rats were repeatedly exposed (6h/day, 5d/wk for 13 weeks) to 20, 41, or 71 ppm (120, 245, or 425 mg/m^3) EGHE and analyzed for changes in hematological and urological parameters, and for changes in organ and body weights and histopathology. These exposures resulted in decreased body weight and increases in male kidney and female liver weights. The authors considered these changes to be adaptive (and not adverse) since there were no correlative changes in histopathology or serum chemistry (Klonne et al., 1987). The changes in liver enzymes in animals exposed to 71 ppm (425 mg/m^3) are difficult to interpret since levels of 3 out of 4 enzymes were decreased and only 1 out of 4 was increased. A dose-dependent increase in urogenital wetness was observed in females, and in the males at the highest exposure.

No effects on red blood cells or histological changes in the liver or kidney were noted at concentrations up to and including the highest concentration tested (71 ppm or 425 mg/m^3). Red blood cell toxicity and histopathological changes in the liver and kidney were not seen in rats exposed for 13 weeks with up to 71 ppm (425 mg/m^3) EGHE by inhalation, suggesting that this material is not as potent a hemolytic agent as EGBE.

Table 4.3.1. Repeated Dose Toxicity Test by Inhalation with EGHE 112-25-4

Inhalation Studies	NOAEL	LOAEL	Effects	References
Subchronic, F344 rat (13 wk, 6 hr/d, 5 d/wk; 0, 20, 41, 71 ppm (120, 245, 425 mg/m^3)	245 mg/m^3 (41 ppm)	425 mg/m3 (71 ppm)	@ 20 ppm: urogenital wetness & increased kidney weight @ 41 ppm: decreased body weight, increased kidney and liver weight, & urogential wetness @ 71 ppm: decreased bw, increased kidney and liver weight, ↓ AST, ALT, SDH,↑ ALP	Klonne et al., 1987
Pregnant F344 rats (0, 20, 40, 80 ppm) on gd 6 to 15, gd 21 analysis)	20 ppm	40 ppm	Maternal toxicity: transient weight gain reduction	Tyl et al., 1989
Pregnant NZW rabbits (0, 20, 40, 80 ppm) on gd 6 to 18, gd 29 analysis)	40 ppm	80 ppm	Maternal toxicity: transient weight gain reduction. No fetal effects reported.	Tyl et al., 1989

[a]No observable adverse effect level (systemic effects). Dose is in ppm (for inhalation experiments).. AST = aspartate aminotransferase, ALT = alanine aminotransferase, SDH = sorbitol dehydrogenase, ALP = alkaline phosphatase.

Although the effects on the kidney were not dose-dependent, liver weights increased in a dose-dependent manner and were not reversed after 4 weeks of recovery in animals exposed to 71 ppm. Therefore, the reported NOAEL was 41 ppm (245 mg/m^3) with a LOAEL of 71 ppm.

5 Derivation of Interim Acute REL (1-hour exposure)

No studies of short-term exposure to EGHE were located that were appropriate for the derivation of an acute REL. While an LC_{50} was reported, this value represents the upper limit for acute exposures that are compatible with survival without regard to protecting health. As such LC_{50} values are not the preferred basis for the derivation of an acute REL, which requires consideration of effects much less severe than lethality.

In the course of an 8-hour exposure, intermittent spikes in exposure levels are included in the time-weighted average addressed with the 8-hr REL. The values associated with 8-hr RELs are typically lower than allowed for acute 1-hr exposures, due to the longer exposure duration and possibility of recurring exposures. Therefore application of the 8-hr REL to exposure scenarios involving short-term peaks in concentration should be health protective in most cases.

Derivation of Interim 8-hour REL

Study	Tyl et al. 1989
Study population	Pregnant F344 rats
Exposure method	Whole body inhalation of 0, 20, 40, or 80 ppm
Exposure continuity	6 hours/day
Exposure duration	Gestation days 6-15 (~ 10 exposures)
Critical effects	Decreased body weight
LOAEL	240 mg/m^3 (40 ppm)
NOAEL	120 mg/m^3 (20 ppm)
Time-adjusted exposure	$C^n * T = K$, $n = 1$
Extrapolated concentration	64.3 mg/m^3 (120 mg/m^3 * 6/8 * 5/7)
Human concentration adjustment	64.3 mg/m^3 (RGDR = 1; systemic)
LOAEL uncertainty factor (UF_L)	1 (NOAEL observed)
Subchronic uncertainty factor (UF_s)	10
Interspecies Uncertainty Factor	
Toxicokinetic (UF_{A-k})	2
Toxicodynamic (UF_{A-d})	√10
Intraspecies Uncertainty Factor	
Toxicokinetic (UF_{H-k})	10
Toxicodynamic (UF_{H-d})	√10
Cumulative uncertainty factor	2000
8-hour Reference Exposure Level	**32.1 μg/m^3**

The 8-hour Reference Exposure Level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures. This draft 8-hour REL is derived from the study by Tyl et al (1989), in time-pregnant F344 rats exposed by whole body inhalation to 0, 20, 40, 80 ppm (0, 120, 240, 490 mg/m^3) EGHE for gestation day (GD) 6-15 for 6 hours per day for an approximate total of 10 exposures. The animal study has a systemic endpoint of decreased maternal body weight. Gestational parameters examined included numbers of corpora lutea, preimplantation losses, viable implants, numbers of resorptions, and dead fetuses. Surviving fetuses were examined for external, visceral, and skeletal variations. The time adjustment for the 8-hour REL used was 6 h/8 h * 5/7 days/week. A LOAEL uncertainty factor was unnecessary because both a LOAEL (240 mg/m^3) and a NOAEL (120 mg/m^3) was determined for the study.

Significant differences in toxicokinetics between rats and humans are not expected to be large so a value of 2 was used for the interspecies toxicokinetics UF. In the absence of data, a default toxicodynamic UF of √10 was applied. Uncertainty factors for intraspecies variability were 10 for toxicokinetics and √10 for toxicodynamics in the absence of specific data. The cumulative UF is therefore 200, which is divided by the time-adjusted NOAEL for a draft 8-hour reference exposure level of 32.1 $\mu g/m^3$.

6 Other Toxicity

Significant reproductive organ toxicity was not noted in any of the repeated dose studies. No treatment-related evidence of developmental toxicity or teratogenicity were observed (Tyl et al., 1989).

7 Environmental fate and effects

The most significant environmental releases of EGHE are expected to take place during the application or end-use of products containing EGHE. These applications include applying surface coatings, cleaning and printing operations. Level III fugacity modeling indicates that members of this glycol ether category including EGHE will tend to partition to water for the most part and to a lesser extent to air and soil. The biodegradation rate was determined to be 100% after 20 days (ECB, 2000). Furthermore, other data indicate that EGHE biodegrades readily.

Aquatic toxicity tests in combination with ECOSAR modeling indicate that the category members with log Pow values < 1 (EGPE and EGBE) are of low toxicity to fish and aquatic invertebrates (LC/EC50 values are 835 mg/l or greater) and the category members with log Pow values > 1 (EGHE and EGBEA) are moderately toxic to these organisms (LC/EC50 values are approximately 20-300 mg/l) (ECB, 2000).

8 References

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